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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

PONNALURI, PADMASHRI

ART UNIT PAPER NUMBER

1639

DATE MAILED: 04/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/764,163

Applicant(s)

BALINT ET AL.

Examiner

Padmashri Ponnaluri

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 January 2005.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 80-88 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 80-84, 88 is/are rejected.
7) ☒ Claim(s) 85-87 is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment and response filed on 1/24/05 has been fully considered and entered into the application.
2. Claims 1-79 have been canceled and new claims 80-89 have been added by the amendment filed on 8/29/03. Claim 89 has been canceled by the amendment filed on 1/24/05.
3. Claims 80-88 are currently pending and are being examined in this application.

Priority

4. This application claims priority to provisional application 60/175,968 and this application is a CIP of 09/526,106.
5. Claims 85-86 (in-part) may not have the benefit of the filing date of the parent application serial number 09/526,106 (filing date 3/15/00). The N-terminal and C-terminal break points in the circularly permuted β -lactamase, asparagine 52 and serine 53; leucine and glycine 92; glutamine 99 and asparagine 100; lysine 215 and valine; and alanine 227 and glycine 228' claimed in Claims 85-86 has no clear support in parent application serial number 09/526,106. Thus the instant claims has the effective filing date of the instant application filing date 1/16/01.

If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the specification.

It has been noted that the response filed on 1/24/05 has not addressed the priority issue raised in the previous office action.

Specification

6. The objection to the specification disclosure set forth in the previous office action has been withdrawn in view of the amendment to the specification.

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7. The specification has not checked to the extent necessary to determine the presence of all possible minor errors. Applicant's co-operation is requested in correcting any errors of which applicant may become aware in the specification.

Withdrawn Claim Rejections

8. The rejections of claims under 35 USC 112, second paragraph set forth in the previous office action has been withdrawn in view of the amendments to the claims.

9. The new matter rejection set forth in the previous office action has been withdrawn in view of the amendments to the claims.

10. The written description rejection set forth in the previous office action has been withdrawn in view of the amendments. Note this rejection has been rewritten to address the new amendments.

11. The rejection of claims 80-81 over Remy et al (Proc. Natl. Acad. Sci. USA, vol. 96, pp 5394-5399, May 1999), set forth in the previous office action has been withdrawn in view of the amendment to the claims.

12. The rejection of claims 80-88 over Pieper et al (Biochemistry, 1997, 36, 8767-8774) (reference provided by applicants) set forth in the previous office action has been withdrawn in view of the amendment to the claims.

13. The rejection of claims 80-81 over US Patent 6,270,964 B1 (Michnick et al) (reference provided by applicants) set forth in the previous office action has been withdrawn in view of the amendment to the claims.

Maintained Claim Rejections

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14. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

15. Claims 80-88 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 63-66 of copending Application No. 09526,106, for the reasons set forth in the previous office action mailed on 5/5/04.

New Claim Rejections Necessitated by the Amendments

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 80-84, 88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is written description rejection.

To satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

Applicants instant claim 80 is drawn to a polypeptide consisting essentially of a first interactor domain covalently bonded to circularly permuted marker protein through N-terminal, and second interactor domain covalently bonded to the C-terminal of the circularly permuted

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marker, and the circularly permuted marker protein is functionally reconstituted only upon binding of said interactor domain and second interactor domain to a single ligand.

The instant specification working example discloses the circularly permuted β -lactamase, which is covalently linked to either antibody fragments or thioredoxin (interacting domains), which clearly does not provide an adequate representation regarding the open ended polypeptide of the instant claim 80.

The instant specification discloses methods and compositions for interaction-dependent enzyme activation system useful in detecting an interaction between a first protein and second target protein. And the circularly permuted protein or a circular permutation of a protein refers to a protein where the amino and carboxyl terminal segments are interchanged and rejoined with a shorter spacer connecting the original N- and C- termini, and heterologous interactor domains are then fused to in frame to the N- and C- terminal breakpoint. The specification discloses that the 'where the interaction-dependent protein system uses a circularly permuted marker protein, the short spacer linking the fragment pair allows for the functional folding of N- and C-terminal segments into the marker protein of interest. The specification discloses that spacer should be comprised of small, preferably neutral residues.

The specification discloses that the first and second interactor domains may be members of a library. And further the specification discloses method for identifying optimal break-points in a parent protein that provides for a detectable signal. The working examples of the specification discloses that specific break points of enzyme β -lactamase that provide a detectable signal. The specification has not disclosed any other enzymes which are useful as circularly permuted enzymes or the optimal break points of the parental enzymes, such ^{that} the circularly

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permuted enzyme has a detectable signal. The specification discloses that the most proteins which have exposed loops, when cleaved and a spacer or linker is inserted, the resulting enzymes were inactive.

The specification discloses that 'to identify CPs (circularly permutations) of TEM-1- β -lactamase, we inserted a sequence encoding a flexible linker between the C- termini and N-termini of two tandem copies of Tem sequence, and these sequences were screened for activity.' Thus, the specification discloses that experimentation is required to identify a circularly permuted enzyme. The instant claim is drawn to a polypeptide (product) consisting essentially of 'a first interactor domain covalently bonded to a circularly permuted marker protein through N-terminal break point and a second interactor domain covalently bonded to a C-terminal break point of a circularly permuted protein', not to the method of identifying a circularly permuted proteins. The specification discloses methods of identifying circularly permuted proteins, and optimal break points for the detectable signal of the marker proteins.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a A written description of an invention involving a chemical genus, like a description of a chemical species, >requires a precise definition, such as by structure, formula [or] chemical name of the claimed subject matter sufficient to distinguish it from other materials. *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)]. For adequate disclosure, representative examples are required, which provides reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that applicant had in possession of the full scope of the claimed invention. See *In re Riat (CCPA 1964)* 327

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F2d 685, 140 USPQ 471; in re Barr (CCPA 1971) 444F2d 349, 151 US PQ 724 and University of California v. Eli Lilly and Co.

The instant claims are drawn to a polypeptide consisting of 'circularly permuted marker proteins, however do not recite the structure of the 'circularly permuted proteins.' In the instant specification all working examples and the figure 11, and table 4, disclose the circularly permuted β -lactamase with break point at positions L198-E197, which is covalently linked to various other proteins (interactor domain), which clearly does not provide an adequate representation regarding the circularly permuted enzyme, and the polypeptide of the instant claims. Thus, the specification has not provided 'representative number of examples' that would indicate to an ordinary skill in the art that applicant had possession of the broadly claimed polypeptide consisting of circularly permuted marker protein.

Response to Arguments

18. Applicant's arguments with respect to claims 80-88 have been considered but are moot in view of the new ground(s) of rejection.

19. Applicant's arguments filed on 1/24/05 regarding the 'written description rejection' have been fully considered but they are not persuasive.

The written description rejection of record has been with drawn and rewritten to address the newly amended claims (clear claims). Note in the previous claim 'circularly permuted marker proteins' was interpreted as 'circularly marker proteins which were covalently linked to proteins at C-termini and N-termini.'

Applicants argue that according to the case laws 'Enzo, Lilly and Rochester that the written description standard may be met for broad composition claims by disclosing as few as three operable structures.' Applicants further assert that in light of Federal Court Decisions

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outlined above, the seven working examples disclosed in the current specification is more than adequate to meet the written description standards set forth by the Federal Circuit and USPTO. And applicants further assert that 'applicants have provided substantial guidance in the specification regarding the methods of designing, making and testing the claimed polypeptides.'

Applicant's arguments and assertions have been fully considered and are not persuasive. Applicant's arguments regarding the three CAFC decisions, Enzo, Lily and Rochester have been considered. None of the case laws cite that 'as few as three operable structures' would meet the written description rejection.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results

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obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). See MPEP 2163.

Thus, in the instant application disclosure of circularly permuted β -lactamase marker protein in the specification working examples, and figures is not representative of the genus of 'circularly permuted marker proteins' claimed in the instant claims.

Further, the specification only describes method of making the circularly permuted marker proteins and the use of the circularly permuted marker proteins in interaction dependent enzyme activation system.

And further the specification discloses well known circularly permuted proteins. However, the specification discloses that exposed loops of most proteins, whose integrity is essential for stability, and circularly permutation of such polypeptides chain within such loop produce unstable proteins (see i.e., page 67 of the specification). Thus, the circularly permuted proteins are not well known in the art as in the applicants arguments.

Applicants arguments regarding 'applicants were in possession of concrete principles of identifying and producing interaction dependent circularly permuted proteins' have been considered and is not persuasive. Since the instant claims are drawn to products (compositions) comprising circularly permuted proteins, and the specification only discloses circularly permuted β -lactamase marker proteins and circularly permuted β -lactamase marker protein

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covalently linked to interactor domains, applicants arguments are not persuasive. Thus, the claimed invention lacks written description.

20. Applicant's arguments filed on 1/24/05, regarding the Obviousness-type double patenting rejection, have been fully considered but they are not persuasive.

Applicants have requested to hold the rejection until patentable subject matter has been found', which does not obviate the rejection. The rejection has been maintained for the reasons of record.

Allowable Subject Matter

21. Claims 85-87 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padmashri Ponnaluri whose telephone number is 571-272-0809. The examiner is on Increased Flex Schedule and can normally be reached on Monday through Friday between 7 AM and 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


PADMASHRI PONNALURI
PRIMARY EXAMINER

Padmashri Ponnaluri
Primary Examiner
Art Unit 1639

18 April 2005